660.51
S993

THE JOHN CRERAR LIBRARY

MAY 14 1958

Volume 30 • 1958 • Number 1

Organic Chemical Bulletin

DPi

Address inquiries to
Eastman Organic Chemicals Dept.
Distillation Products Industries
Division of Eastman Kodak Company
Rochester 3, N. Y.

PUBLISHED BY THE RESEARCH LABORATORIES OF THE EASTMAN KODAK COMPANY

CONTINUOUS REACTORS FOR PREPARING ORGANIC CHEMICALS

By C. F. H. Allen, J. R. Byers Jr., W. J. Humphlett, and D. D. Reynolds*

For over a hundred years, organic substances have been prepared following essentially the same manipulative procedures which utilize the same types of apparatus—heated or cooled containers with condensers, stirrers, dropping funnels, thermometers, and the like. In spite of its long use, the "batch process" leaves much to be desired. Its most serious fault is the long period of time involved in the warming up and cooling down of the reaction mixture. Heat-sensitive components are, thus, subject to decomposition, as shown by the formation of color and "tar." Secondary reactions involving the desired product also take place, reducing the yield, increasing the difficulties of purification, and giving rise to by-products. Less important disadvantages are the limited capacity, the space required, close fitting of adjunct equipment, etc.

A "continuous reactor" has been devised in these Laboratories to circumvent these undesirable features (1-9). It is called "continuous" because the reaction proceeds as long as the reactants are supplied and products are removed. The new apparatus is of general utility and is relatively inexpensive. The laboratory-size model is easily set upon on a single iron stand and is built of standard parts (ground-glass ball-and-socket joints are easier to use than the more common standard-taper type). Simple modifications to permit introduction of a gas, countercurrent operation, or irradiation allow many types of reaction. The capacity can be enlarged by increasing the size or by using additional units in a series. Larger-sized models are readily built, with larger-diameter tubes or even Pyrex-glass pipe, yet they occupy but little more space.

The starting materials can be liquid or solid; the latter can be (1) melted by external heating of the addition funnel, (2) dissolved in a minimum of solvent (which may later have to be removed), or (3) admitted as a powder (not easily done with ordinary laboratory equipment). The filtrate from which a solid product has been removed can be re-used to dissolve starting materials.

The general form of the apparatus (1,4a,5) is shown in Fig. 1. Essentially, it consists of several sections of an externally heated, 2- by 50-cm. packed column having a Y-tube at the top and a receiver at the bottom. One arm of the Y bears an addition

*Research Laboratories, Eastman Kodak Company, Rochester 4, New York.

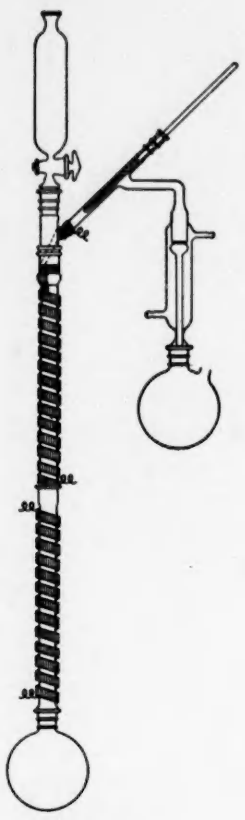

Figure 1

funnel (or two if needed). The constant-rate addition funnel (2) is especially useful here, as it minimizes the need of frequent attention; the latest modification has, above the stopcock, a ground-glass joint which accepts any size of reservoir. The other arm of the Y bears a stillhead leading to a take-off condenser, which serves to condense volatile products. The column can even serve as a simple still. The packing can be varied to suit the size of column, product, rate, and other conditions. The smaller columns are conveniently filled with glass helices, stainless-steel sponge, or prepared fillings (e.g., Amberlites); larger-size columns employ Berl saddles. Each section of column is wrapped with a 275-watt, flexible heating tape (6 ft. by 0.5 in.) connected to variable transformers on 110-volt lines. This form of the reactor may be modified to admit a gas by inserting a lead-in Y-tube between the receiver and the column or between any two adjacent sections. It can even be used to effect two consecutive reactions by introducing a Y between sections. Thus, an acid-catalyzed reaction might take place in the upper section and the pH raised by admitting a base to the lower section.

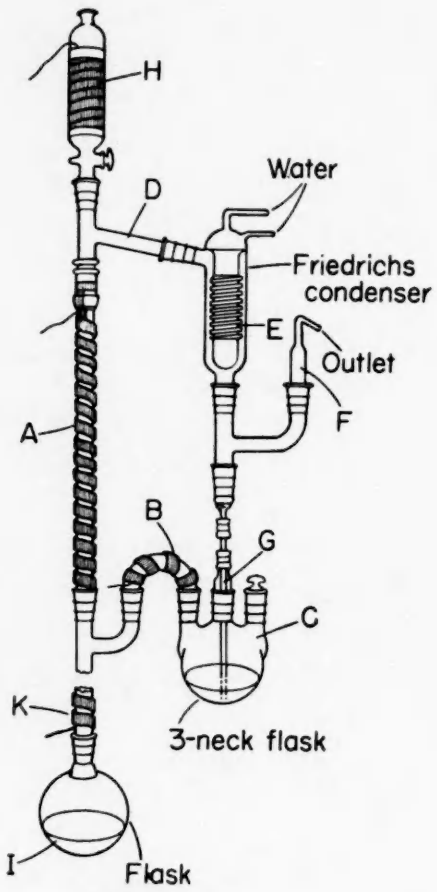

Figure 2

A second modification (1,4b,7), called the "tangential reactor" because one of the components flows down the column countercurrent to a gas, is shown in Fig. 2. This is especially useful for preparing acid chlorides with circulating thionyl chloride; it is essential that the tube from the lower end of the condenser extend to the bottom of the boiling flask. The leg removes any dissolved gaseous product, such as excess thionyl chloride. When operated properly, there is no unused acid, as shown by infrared examination of the product. This apparatus is also useful when it is desired to limit the volume of solvent used. Acetone is useful as the circulating liquid for many reactions. Other special variations of the reactor are possible, but these have a more limited versatility. Electrically heated mantles (not shown in the figures) are employed if needed.

Not only have two or more reactors in series been set up in these Laboratories to make use of consecutive reactions, but controls have been attached to render the entire arrangement essentially automatic. A triangle receiver (3) makes it possible to remove distillate from a vacuum distillation without breaking the vacuum.

The continuous reactor is most useful with rapid reactions but can be employed for those that proceed at a slower rate by increasing the time of contact with heated surfaces; this is accomplished by a finer packing, additional sections, or recirculation. The reaetion time depends upon the size of packing, the temperature, and the viscosity of the reaction mixture. For instance, an alcoholic solution passes through a 2- by 100-cm. column packed with ¼-in.

glass helices in 45 sec.; xylene passes through the same column packed with ⅛-in. glass helices in 3 min., whereas 6 min. are required for a mixture of benzaldehyde and ethyl malonate. Acetic acid passes through either a 4-in. by 5-ft. or 2-in. by 8-ft. column packed with ½-in. or ¼-in. Berl saddles, respectively, in 45 sec. The capacity of such a 4-in. column, which occupies less than a 3-ft. square area, is 3-10 kgm. per hour.

The most surprising discovery resulting from the use of these reactors is the rate at which many reactions occur. Most organic reactions are considered to be slow and to require several hours to attain reasonable yields, yet high yields have been obtained in this apparatus when the dwelling time varied from 30 sec. to 6 min. This behavior may be attributed to the very large surface afforded by the packing. In the case of equilibria which can be displaced by removal of a volatile product, the current is adjusted so that distillation occurs. Of nearly equal interest is a reaction involving five components: azlactone formation has given a 73% yield of a product, the melting point of which is unchanged by recrystallization.

This short contact time with heated surfaces results in fewer side reactions, a better-quality product, and very often a higher yield. Low yields can usually be improved by a study of conditions; if the reaction is slow, an increase in reaction time may be effected, as already indicated.

A few illustrations of actual preparations will serve to show the versatility of this apparatus. Procedures and details of some operations will be found in the references. The actual yields and rates are determined by working up an aliquot. It is most convenient to "calibrate" the apparatus for each solvent, by admitting it to the column which is heated so that it just distills, then reducing the current just enough to prevent distillation. The setting on the voltage regulator is then recorded for future use with that solvent. The reaction media most commonly used are alcohol, glacial acetic acid, and xylene. Low yields are usually accounted for by unused components (too rapid flow rate), but may also be due to by-products. Occasionally, it will be found that the reaction does not give the product expected, but that a side reaction predominates. Double decomposition reactions in which an insoluble inorganic salt is formed are not very satisfactory, and a column packed with Berl saddles is essential. Xylene is the favored solvent here, since the salt is more likely to separate in a slimy condition and to emerge gradually at the lower end.

Amide formation from an acid chloride and aromatic amine is very rapid. An amine hydrochloride can even be used if the tangential reactor is employed, with acetone as the circulating solvent and dimethylaniline as the acid acceptor. Pyrazolone formation requires a two-step reactor, with an addition tube inserted between the upper and the lower sections. An absolute alcoholic solution containing ethyl β-ethoxy-β-iminopropionate, a hydrazine, and a little acetic acid for a catalyst is admitted at the top, and alcoholic sodium ethoxide in slight excess at the junction. The yield is 75% when the rate is 0.3 mole per hour.

In the tangential reactor, the yields of palmitoyl, oleoyl, and ricinoleoyl chlorides have been practically quantitative. At the rate of 0.4 mole per hour, the dwelling time of the acid is less than 5 min. when ⅛-in. glass helices are employed as packing. Solid acids can be melted or dissolved in the acid chloride already at hand. To show the versatility of this modified reactor, trimethylene bromide was circulated while diethyl malonate and sodium methoxide in octyl alcohol were admitted from a heated addition funnel. (The sodium bromide which precipitated would have clogged the column in time.) One-third mole of ester over a 35-min. period gave an 85% yield of distilled tetraethyl trimethylenebismalonate. Side-

Table I. Comparative Yields of Two Procedures

Reaction	*Components*	*Rate*	*Yield, %*	*M.P., °C.*	*Comments*
Amide formation[a] $C_6H_5COCH_2CONHR$	Ethyl benzoylacetate	0.5 mole/15 min.	90	104-105	Cont. } $R = C_6H_5$
	$C_6H_5NH_2$	0.2 mole/1 hr.	76	104-105	Batch }
		0.33 mole/1 hr.	89	178-180	Cont. Excess ester used as solvent.
	$4\text{-}NO_2\text{-}2\text{-}OCH_3C_6H_3NH_2$	0.22 mole/1 hr.	81	130-150	Batch 65% yield, if purified to same m.p.
Azlactone	C_6H_5CHO, Hippuric acid, Ac_2O, AcOH, AcONa	1 mole/45 min.	73	166-167	Cont.
		1 mole/225 min.	64	165-166	Batch
Ethyl benzalmalonate	C_6H_5CHO, $CH_2(COOC_2H_5)_2$ piperidine benzoate	0.7 mole/30-90 min.	81-82		Cont.
		0.63 mole/16 hr.	25		Batch Reflux
		0.63 mole/18-48 hr.	86-90		Batch Azeotroping
		0.63 mole/40 min.	14		Cont. Amberlite 1R-4B packing
Phenoxy esters $ArOCHClCOOR$	A sodium phenoxide	0.5 mole/35 min.	62		Cont.[b] $Ar = C_6H_5$
	An α-haloester	0.25 mole/55 min.	81		Cont.[b] $Ar = C_{12}H_{25}C_6H_4$
	solvent	0.1 mole/20 min.	79		Cont.[b] $Ar = (C_5H_{11})_2C_6H_3$
		0.2 mole/6 hr.	89		Batch
Michael reaction	$C_6H_5CH=CHCOC_6H_5$ in alc.	1.1 mole/1.5 hr.	83	71-72	Batch
plus	1. $CH_2CNCOOCH_3$	0.71 mole/1 hr.	91.5	71-72	Cont. 45 sec. in column!
(and OH^-)	2. $CH_2(COOC_2H_5)_2$	0.38 mole/1 hr.	95	105	Cont. 45 sec. in column!
Isocyanato esters	$HClNH_2CHCOOR$		80		Batch 50 g. amine HCl used
	$(CH_2)_2COOR$		60		Batch 100 g. amine HCl used
	$COCl_2$		30		Batch 400 g. amine HCl used
	solvent ($C_3H_5Cl_3$)		93		Cont. 1 kg. per day in 2-in. col. 97% yield with butyl ester

[a] Phenyl esters give 78-84% yield.
[b] 1/4-in. Berl saddle packing.

chain chlorination, using sulfuryl chloride and ultraviolet radiation (1,8), and the bromination of nitriles (9) require additional modifications. A number of examples, to illustrate the scope of the reactor and to compare yields by the batch process, are given in the table.

Possible applications of these reactors appear to be almost unlimited, although some limitations (e.g., salt separation) have already been mentioned. A little study may be required to determine the optimum conditions. For instance, alkyl bromide synthesis (HBr method) appears feasible: a single run, using two graduated addition funnels (one containing butyl hydrogen sulfate and the other 48% HBr) gave a 70% yield of butyl bromide at the rate of 150 gm. per hour. Bromination of aliphatic acids is too slow to compete with the 96% yield of acid anhydride-catalyzed batch brominations. Ester formation is also slow, but could undoubtedly be made practical by recirculation of effluent. For example, γ-chloropropyl acetate has been prepared in 72% yield in three passes (at the rate of 200 gm. per hour), whereas the batch process gives a 90-95% yield in 9 hr. An exploratory cyclization using diethyl ethoxymethylenemalonate and aniline in 1-methyl-naphthalene gave a 35% yield of the quinoline derivative expected.

A comparison of typical continuous and batch preparations is summarized in the table. By considering also the size of the reaction vessels, a stricter interpretation might report the "rate" in terms of moles per hour per liter. Since the volume of a continuous reactor is small, the reactors would appear even more favorable.

While these reactors are likely to be most useful when large amounts of substances are required, e.g., start of a research or development program, they can be equally useful for class preparative work, in which situation students might take turns in obtaining products quickly for future manipulative study. In view of the surprising simplicity of these reactors, their wide versatility, and their unique advantages in numerous cases, it appears that one of this general type could well be used advantageously as a part of the standard equipment of many preparative laboratories.

References

1. Allen, C. F. H., Byers Jr., J. R., Humphlett, W. J., and Reynolds, D. D., *J. Chem. Education*, *32*, 394-399 (1955).
2. Humphlett, W. J., *Org. Chem. Bull.*, *27*, 6 No. 3 (1955).
3. Humphlett, W. J., *Anal. Chem.*, *29*, 1241-1242 (1957).
4. Cason, J. (*editor*), "Organic Syntheses," Vol. 37, John Wiley and Sons Inc., New York, N. Y., 1957, (a), 2, (b) 66 (1957).
5. Humphlett, W. J. (To Eastman Kodak Co.), U. S. 2,780,632 (1957).
6. Humphlett, W. J. (To Eastman Kodak Co.), U. S. 2,784,225 (1957).
7. Humphlett, W. J. (To Eastman Kodak Co.), U. S. 2,808,420 (1957).
8. Reynolds, D. D.; Allen, C. F. H. (To Eastman Kodak Co.), U. S. 2,811,486 (1957).
9. Allen, C. F. H., Davis, T. J., Humphlett, W. J., and Stewart, D. W., *J. Org. Chem.*, *22*, 1291-1295 (1957).

New Eastman Organic Chemicals

5048	Allyl Ether BP 93-94°	100 g.	$ 2.65	500 g.	$ 8.60
	$CH_2:CHCH_2OCH_2CH:CH_2$ . . . MW 98.15				
7536	Benzhydrazide MP 113-115°	25 g.	2.40	100 g.	7.75
	$C_6H_5CONHNH_2$ . . . MW 136.16				
7502	iso-Butylbenzene BP 172-174°	10 g.	3.20	25 g.	6.65
	$(CH_3)_2CHCH_2C_6H_5$ . . . MW 134.22				

New Eastman Organic Chemicals *(Continued)*

P 7514	3-Chloro-N,N-dimethyl-1-propylamine Hydrochloride (Pract.)	100 g.	..	4.00	500 g.	.. 15.45
	$CH_2ClCH_2CH_2N(CH_3)_2 \cdot HCl$ . . . MW 158.08					
7571	3-(4-Chloro-2-hydroxyphenylazo)-4,5-dihydroxy-2,7-naphthalenedisulfonic Acid Disodium Salt—(reagent for Ca in blood serum)	10 g.	..	4.05	25 g.	.. 8.80
	$Cl(HO)C_6H_3N{:}NC_{10}H_3(OH)_2(SO_3Na)_2$ . . . MW 518.84					
T 4603	2,5-Dihydroxy-*p*-benzoquinone (Techn.)	250 g.	..	3.60	1 kg.	.. 11.00
	$(HO)_2O{:}C_6H_2{:}O$ . . . MW 140.10					
7545	Dimethylfurazan MP -8° to -6°	5 g.	..	2.55	25 g.	.. 9.10
	$CH_3C{:}NON{:}CCH_3$ . . . MW 98.11					
7524	N,N-Di-iso-propylacetamide BP 71-73°/6 mm.	25 g.	..	2.20	100 g.	.. 6.45
	$CH_3CON[CH(CH_3)_2]_2$ . . . MW 143.23					
7528	N,N-Di-iso-propylpropionamide BP 76-77°/6 mm.	25 g.	..	2.20	100 g.	.. 6.45
	$CH_3CH_2CON[CH(CH_3)_2]_2$ . . . MW 157.26					
7538	Ethylurea MP 94-96°	10 g.	..	3.05	25 g.	.. 6.25
	$C_2H_5NHCONH_2$ . . . MW 88.11					
7506	DL-2-Methylbutyryl Chloride BP 116-118°	25 g.	..	2.50	100 g.	.. 7.60
	$CH_3CH_2CH(CH_3)COCl$ . . . MW 120.58					
3075	3-Methylcyclohexanone BP 167-169° . .	100 g.	..	4.75	500 g.	.. 19.20
	$CH_2CH(CH_3)(CH_2)_3CO$ . . . MW 112.17					
7544	*n*-Octyl Nitrite BP 52-53°/6 mm.	25 g.	..	2.05	100 g.	.. 5.85
	$CH_3(CH_2)_6CH_2ONO$ . . . MW 159.23					
7542	2,4,5,7-Tetrabromo-1,8-dihydroxyanthraquinone MP 324-326° (reagent for boron)	5 g.	..	2.95	25 g.	.. 11.05
	$Br_2(OH)C_6HCOC_6HBr_2(OH)CO$ . . . MW 555.85					
4508	Toluene-3,4-dithiol MP 28-30° (reagent for various heavy metals)	1 g.	..	3.00	5 g.	.. 12.00
	$CH_3C_6H_3(SH)_2$ . . . MW 156.27					

Note: The subject matter contained in this *Bulletin* is for information only, and none of the statements contained herein should be considered as a recommendation for the manufacture or use of any substance, apparatus, or method in violation of any patents now in force or which may issue in the future.